

Before, Between & Beyond Pregnancy
**The National Preconception Curriculum and Resources Guide
for Clinicians**

**Guidance for Preconception Fragile X
Carrier Screening**

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This guidance should not substitute for clinical judgments or expert consultation

Guidelines for Cascade Testing and Genetic Counseling

McConkie-Rosell A, Abrams L, Finucane B, Cronister A, Gane LW, Coffey SM, Sherman S, Nelson LM, Berry-Kravis E, Hessel D, Chiu S, Street N, Vatave A, Hagerman RJ. Recommendations from multi-disciplinary focus groups on cascade testing and genetic counseling for Fragile X-associated disorders. J Genet Counsel 2007;16:593-606.

This paper reports the outcome of a collaborative project whose objective was to develop and disseminate protocols for genetic counseling and cascade testing for the multiple disorders associated with the fragile X mental retardation 1 (FMR1) mutation. These disorders include Fragile X syndrome, fragile X associated tremor/ataxia syndrome (FXTAS), premature ovarian failure (POF) and other associated psychiatric, behavioral and psychological issues. The group also discussed ethical issues surrounding the availability of population screening for FMR1 mutations.

Fragile X syndrome is the most common inherited cause of mental retardation and the most common single gene mutation associated with autism. It is caused by an expanded trinucleotide repeat in the promoter region of the FMR1 gene. Typical alleles have approximately 12-44 CGG repeats. Approximately 1/4000 males and 1/6000 females have a full mutation associated with classic features of fragile X syndrome. A full mutation contains greater than 200 repeats that are partially or fully hypermethylated. This leads to an inactivation of the FMR1 gene and a reduction or absence of the FMR1 gene product, fragile X mental retardation protein (FMRP). Alleles with repeats between 55 and 200 repeats are considered premutation alleles and are present in approximately 1/250 females and 1/800 males. Premutation alleles are typically unmethylated and usually do not result in gene inactivation, but are potentially unstable and may expand from one generation to the next. Alleles with approximately 45-54 repeats, intermediate or grey zone alleles, may or may not be stable upon transmission. Approximately 1/72 to 1/145 people are thought to carry an FMR1 expansion in the intermediate range.

Fragile X associated tremor/ataxia syndrome (FRXTAS) is an adult onset (>50 years of age) neurological condition that develops in at least one third of males with an FMR1 premutation. Symptoms are significantly less frequent and often milder in female premutation carriers. Common findings of FRXTAS include non-resting tremor, ataxia, autonomic dysfunction, executive function deficits, short term memory loss, irritability, neuropathy and for some, dementia. Magnetic resonance imaging (MRI) and radiological features include brain atrophy and white matter disease, particularly involving the middle cerebellar peduncles (MCP). Reported neuropathological findings include eosinophilic intranuclear inclusions in neurons and astrocytes throughout the central nervous system. Psychiatric findings may include anxiety, depression, agitation and dementia. Individuals with FRXTAS are often misdiagnosed with Parkinson's disease, other ataxias, stroke, Alzheimer's disease, multiple sclerosis and other conditions. It has been estimated that approximately 2.2-5.1% of individuals with neurological diagnoses, including ataxia and multiple system atrophy (MSA) carry an FMR1 premutation.

Approximately 15-22% of females who carry the FMR1 mutation are expected to experience premature ovarian failure (POF), also termed "fragile X associated primary ovarian insufficiency." Women with an FMR1 premutation are also thought to be at increased risk for menopause at a younger age with or without characteristics consistent with a premature decline in ovarian function, such as decreased inhibin B and elevated follicle stimulating hormone (FSH) levels. An FMR1 premutation can be found in approximately 0.8-7.5% of women with idiopathic sporadic POF and up to 13% of women with a family history of POF and no known family history of fragile X syndrome.

The most commonly noted behavioral symptoms in individuals with full FMR1 mutations include autism spectrum disorders, attention deficit/hyperactivity disorder and anxiety, though the yield of fragile X diagnoses among people in the general population with these common symptoms is likely to be low. Less common psychiatric symptoms associated with fragile X syndrome include selective mutism, obsessive-compulsive features and psychosis. Approximately 70% of females with a full FMR1 mutation do not have mental retardation, but may present with psychiatric symptoms including anxiety and mood instability. Individuals with a diagnosis of FXTAS are more likely to display psychiatric findings including depression, anxiety and dysinhibition that may eventually evolve into front-subcortical dementia. There is some evidence to suggest that premutation carriers may be at increased risk for anxiety, obsessive-compulsive disorder, depression, social deficits and autism spectrum disorders, though this association remains controversial.

Due to the prevalence of FMR1 mutations and premutations in the general population, routine preconception and pregnancy screening has been suggested. A significant number of women in the general population could be reached if screening were offered at appointments for routine gynecological, infertility and primary care. Advantages of general population screening includes the availability of family planning and education for the individual and other family members should an FMR1 mutation or premutation be discovered, risk management for FXTAS and POF after the identification of a premutation, and relief following a negative test result. Disadvantages can include

increased anxiety and a change of expectations surrounding future parenthood and health, increased stress in present or future relationships, and negative emotions related to positive carrier status. The authors stress the importance of pre-test and post-test counseling to the success of a general population screening program. Increased community awareness and education are critical to providing appropriate patient care.

At this time, the authors recommend newborn screening for fragile X syndrome be performed only as part of a well designed research study. It is important to assess the current state of existing developmental services and to build an infrastructure to ensure the appropriate services can be provided when FMR1 mutations or premutations are identified.

Overall, it is important for clinicians to be familiar with the variable clinical presentations of FMR1 mutations, including classic fragile X syndrome, FXTAS and POF. Because the diagnosis of an FMR1 mutation has significant implications for family members in addition to the proband, genetic counseling is essential following the identification of an FMR1 mutation or premutation, regardless of ascertainment.